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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,810	03/21/2001	Richard Anthony Flynn	21025-11	8199

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EXAMINER	
BENNETT, RACHEL M	
ART UNIT	**PAPER NUMBER**
1615	7

DATE MAILED: 12/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/787,810	Applicant(s) FLYNN ET AL.	
	Examiner Rachel M. Bennett	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-25 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,23-25 and 29* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The examiner acknowledges receipt of Amendment A filed 7/22/02 and Supplemental Amendment B filed 8/14/02.

Claims 1-21, 23-25 and 29 are pending.

Specification

Claim Objections

1. Claim 13 objected to because of the following informalities: Claim 13 states "according to any claim 4". It is suggested applicants delete "any". Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 is indefinite because Applicants do not clearly define the diameter of micronized particles. The instant claims read "a diameter of less than 10 micrometers". Thus, including zero. It is suggested, Applicants indicate a lower range for the particle size.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claim 1-21, 23-25, 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al. (US 5641510), and further in view of Rose et al. ("Evaluation of Sodium Colistmentate Aerosol") and Catchpole et al. ("A reassessment of in-virtto activity of colistin sulphomethate sodium").

Clark discloses capsules (such as hard gelatin, cellulose and plastic capsules) containing pharmaceutical powders which are administered to a patient via inhalation are treated so as to increase the effective amount of the pharmaceutical agent reaching the respiratory system of the patient. The capsules are coated internally with a lubricant during manufacture. The lubricant-coated capsule is dusted internally with a dusting agent such as a salt (e.g. sodium chloride) or a sugar (e.g. lactose, mannitol, trehalose or sucrose) prior to inserting the pharmaceutical powder inside the capsule (see abstract). This method serves to improve aerosol delivery of the pharmaceutical powder to the patient. The term "pharmaceutical powder" refers to a powder containing at least a pharmaceutical compound and, optionally, a pharmaceutical acceptable carrier or excipient. The pharmaceutical powder is generally administered to the respiratory tract of the patient in the form of an aerosol. Examples of pharmaceutical compounds which might usefully be incorporated into the hard gelatin capsule include pharmaceutical polypeptides, anti-bacterials and antibiotics (see cols. 5 and 6). A mixture of pharmaceutically compound particles and an excipient can form the pharmaceutical powder. Examples of pharmaceutically acceptable carriers or excipients include, but are not limited to, salt compounds (e.g. sodium chloride) or sugar compounds (e.g. glucose, fructose, lactose, mannitol, trehalose and sucrose). Other conventional agents such as those which are conventionally incorporated into dry powder inhalant compositions may be present in the pharmaceutical powder. The average particle size

of the particles of the pharmaceutical powder containing the therapeutic agent is preferably in the range 0.1 to 20 micrometers, more preferably 1 to 6 micrometers. Typically, at least 50% of the particles will be of a size which falls within this range, although the presence of significant quantities of fine material is contemplated within the scope of the invention (see col. 5 lines 1-13). The pharmaceutical powder having the desired particle average particle size can be prepared by dry mixing the pharmaceutical compound and the excipient. Clark does not teach the antibiotic to be colistin sulphomethate sodium.

Rose discloses the evaluation of sodium colistimethate aerosol in gram-negative infections of the respiratory tract. Sodium colistimethate (SCM), the methane sulfonate derivative of colistin, is bacterial and active against many strains of gram-negative bacilli. SCM is used for aerosol therapy, dissolved in sterile water and administered by intermittent positive pressure breathing instruments yielding a particle size of 1-7 microns. SCM in aerosol form is well tolerated by all patients except one, who in addition to obstructive pulmonary disease, suffered from angina pectoris. Daily dosages ranging from 75 to 300 mg, given one to three times a day, given one to three times a day, resulted in pathogen free sputum cultures in 60% of the patients. The results of the study indicate that aerosolized SCM is well tolerated and effective in eradicating or suppressing susceptible gram-negative organisms carried in the respiratory tract of patients with underlying pulmonary disease.

Catchpole discloses a reassessment of in-vitro activity of colistin sulphomethate sodium. Colistin is known to be used as inhaled therapy for treatment of infection by *Pseudomonas aeruginosa* in patients with cystic fibrosis. The in-vitro activity of colistin sulphomethate sodium was compared with that of other commonly used antibiotic agents against 377 recent

clinical isolates of Gram-negative bacterial, including 94 strains of *Pseudomonas aeruginosa* from patients with cystic fibrosis. The results show that colistin remains a useful antimicrobial agent against Gram-negative bacteria, particularly those strains which are resistant to more commonly used antibiotics (see abstract).

Absent unexpected results, it would have been obvious to one of ordinary skill in the art at the invention was made to have modified the composition of Clark by substituting colistin sulphomethate sodium as taught by Rose and Catchpole for the antibiotic taught by Clark because of the expectation of producing an composition that is "well tolerated and effective in eradicating or suppressing susceptible gram-negative organisms carried in the respiratory tract of patients with underlying pulmonary disease" as taught by Rose and provide an added advantage of "a useful antimicrobial agent against Gram-negative bacteria, particularly those strains which are resistant to more commonly used antibiotics" as taught by Catchpole. Colistin sulphomethate sodium is known to be in micronized particles as taught by Rose. Therefore, the expected result would be micronized particles, with the desired diameter mixed with a carrier in the desired ratio of colistin sulphomethane sodium to carrier.

Response to Arguments

6. Applicant's arguments filed 7/22/02 have been fully considered but they are not persuasive.

Rejections under 35 USC 103(a)

Applicants argue neither Clark, Rose nor Catchpole teach micronized powder particles of colistin SMS. Rather Clark teaches that pharmaceutical powders may be included within a

capsule treated with a lubricant. Moreover, neither Rose or Catchpole references teach the delivery method of colistin SMS.

The examiner refers to Clark, wherein capsules (such as hard gelatin capsules comprising opaquing agents) containing pharmaceutical powders which are administered via inhalation are treated so as to increase the effective amount of the pharmaceutical agent reaching the respiratory system of the patient. Furthermore, a carrier or excipient is included with the pharmaceutical powder. Carriers include fructose, lactose, mannitol, trehalose, and sucrose. Other compounds can be present in the pharmaceutical powder where required or desired such as bronchodilator (e.g. isoprenaline, rimiterol, ephedrine, ibuterol, isoetharine, fenoterol, carbuterol or clinbuterol) (see col. 6 lines 12-31). Thus, Clark teaches a capsule for inhalation comprising a pharmaceutical powder with a particle size of more preferably 1 to 6 micrometers, a carrier and a bronchodilator. Rose teaches sodium colistimethate sterile powder used in an aerosol in a particle size of 1-7 microns. Therefore, it is the position of the examiner it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute sodium colistimethate taught by Rose and Catchpole for the pharmaceutical powder taught by Clark with the expectation of obtaining of producing an composition that is "well tolerated and effective in eradicating or suppressing susceptible gram-negative organisms carried in the respiratory tract of patients with underlying pulmonary disease" as taught by Rose and provide an added advantage of "a useful antimicrobial agent against Gram-negative bacteria, particularly those strains which are resistant to more commonly used antibiotics" as taught by Catchpole. Colistin sulphomethate sodium is known to be in micronized particles as taught by Rose. Therefore, the expected result

would be micronized particles, with the desired diameter mixed with a carrier in the desired ratio of colistin sulphomethane sodium to carrier.

While applicants argue the powder in Rose is intended to be dissolved in water and the state of the art at the time the invention and in view of the cited references would not have led one of ordinary skill in the art to the instant invention. The examiner disagrees. At the time the invention was made, dry powder formulations, which are delivered by a dry powder inhaler or by a metered dose inhaler, were well known in the art (see art of interest). Therefore, it would have been obvious to substitute the sodium colistimethate taught by Rose and Catchpole for the pharmaceutical powder taught by Clark. Thus, the rejection is maintained.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel M. Bennett whose telephone number is (703) 308-8779. The examiner can normally be reached on Monday through Friday, 8:00 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (703) 308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3592 for regular communications and (703) 309-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

R. Bennett: RMB
November 27, 2002

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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